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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,872	03/22/2002	Izaak den Daas	MERCK 2394	6738
23599	7590	02/05/2004		
MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			EXAMINER NICHOLS, CHRISTOPHER J	
			ART UNIT 1647	PAPER NUMBER

DATE MAILED: 02/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/088,872	Applicant(s) DEN DAAS ET AL.	
	Examiner Christopher Nichols, Ph.D.	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 4-8, 10 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 9 is/are rejected.
- 7) ☒ Claim(s) 2 and 3 is/are objected to.
- 8) ☒ Claim(s) 1-11 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 March 2002 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s) _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-3 and 9) in the Response filed 9 December 2003 is acknowledged. The traversal is on the ground(s) that a search of Groups I-IV would be co-extensive and would not represent a serious search burden for the Patent Office. This is not found persuasive because Groups I, II, III, and IV each and singly encompass special technical features, each which is not shared by the other for the reasons as set forth in the previous Office Action (12 August 2003). Thus to search and examine all four Groups represents a search burden on the Examiner and therefore lack of unity is found. Claims **4-8** and **10-11** are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.
2. The Amendment filed 22 March 2002 has been received and entered in full. Claims 7, 8, and 10 have been amended.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pp. 16 line 11; pp. 27 line 3). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.
4. The disclosure is objected to because of the following informalities: missing letters "effectiv " (pp. 2 line 1), "cultur d" (pp. 2 line 36), "dos s" (pp. 3 line 3), "r sponsible" (pp. 4 line 35), "gen tic" (pp. 4 line 36), "s quence" (pp. 5 line 30), " specially" (pp. 6 line 32), "sequ nce"

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(pp. 8 line 2), “ xisting” (pp. 11 line 35), “sequenc “ (pp. 11 line 35), “Th xpression” (pp. 12 line 35), “Gen rally” (pp. 12 line 36), “v ctor” (pp. 13 line 1), “us d” (pp. 13 line 2), “subj ct’s” (pp. 14 line 1), “inv ntion” (pp. 15 line 1), “G net” (pp. 15 line 33), “dis ase” (pp. 17 line 33), “nzymes” (pp. 19 line 2), “polynucleotid s” (pp. 20 line 2), “ xpression” (pp. 22 line 2), “s quences” (pp. 23 line 2), “sequ nce” (pp. 24 line 2), “sam or v ry similar length, or ov r shorter, “ (pp. 25 line 34), “Figur Leg nds:” (pp. 30 line 1), “Futher r Exampl s” (pp. 31 line 1), “prim r” (pp. 33 line 2); Undefined asterisk “*Calcium” (pp. 6 line 9, pp. 9 line 18), (D13S168-D13S153)*” (pp. 16 line 12); double period “methods..” (pp. 7 line 15), “SEQ ID NO:1..” (pp. 24 line 2). Appropriate correction is required.

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: “Exp 1” and “Exp 2”. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

6. Claim 1 is objected to because of the following informalities: missing space between words “thesequence” (line 2). Appropriate correction is required.

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7. Claims 2 and 3 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated polypeptide comprising SEQ ID NO: 2, consisting of SEQ ID NO: 2, and/or encoded by SEQ ID NO: 1*, does not reasonably provide enablement for *fragments, sequence variants, and other variants thereof*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.
9. The claims are drawn to fragments, variants, and sequence altered proteins based on SEQ ID NO: 2. The language of said claims does not include any specific structure or activity which must be retained.
10. The specification teaches that SEQ ID NO: 1 encodes SEQ ID NO: 2 which is a Ca^{2+} -binding protein.

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11. The specification fails to provide any guidance for the successful diagnosis or assessment of fragments and variants of SEQ ID NO: 2, and since resolution of the various complications in regards to predicting the effects of mutations such as truncation and substitution in proteins is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations SEQ ID NO: 2 fragments and variants to correlate with SEQ ID NO: 2 activity. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

12. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a altering a polypeptide based solely on its prophetic guidance as highly problematic (see MPEP §2164.03). Thus, although the specification prophetically considers and discloses general methodologies of mutating SEQ ID NO: 2, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

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13. The following references are cited herein to illustrate the state of the art of protein biochemistry and Ca^{2+} -binding proteins.

14. Regarding derivatives and fragments of SEQ ID NO: 2, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a

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starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research 10:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. 18(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics 14(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology 15:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics 15(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics 12(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

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15. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from prophetic guidance to mutating and/or varying protein sequence as exemplified in the references herein.

16. Claims 1 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to polypeptides having at least 95% sequence identity with SEQ ID NO: 2. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

17. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is

a polypeptide comprising SEQ ID NO: 2 and polypeptides encoded by SEQ ID NO: 1. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

18. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

19. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF’s were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

20. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2 and the polypeptide encoded by SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is

reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

21. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by US 6,071,721 B1 (6 June 2000) Tang *et al.* US 6,071,721 teaches a nucleic acid which shares 99.7% sequence homology with SEQ ID NO: 1 of the instant application thus meeting the limitations of “variants of such polypeptides in (a)” of claim 1 (sequence listing, SEQ ID NO: 2 therein). US 6,071,721 also teaches a polypeptide which shares 100% sequence homology with SEQ ID NO: 1 of the instant application as well as “variants” and “fragments” thus meeting the limitations of claim 1 (b)-(d), 2, and 3 (sequence listing, SEQ ID NO: 1 therein; Col. 2 lines 33-43; Col. 9 lines 55-67).
22. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by US 6,365,371 B1 (2 April 2002) Tang *et al.* US 6,365,371 teaches a nucleic acid which shares 99.7% sequence homology with SEQ ID NO: 1 of the instant application thus meeting the limitations of “variants of such polypeptides in (a)” of claim 1 (sequence listing, SEQ ID NO: 2 therein). US 6,365,371 also teaches a polypeptide which shares 100% sequence homology with SEQ ID NO: 1 of the

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instant application as well as “variants” and “fragments” thus meeting the limitations of claim 1 (b)-(d), 2, and 3 (sequence listing, SEQ ID NO: 1 therein; Col. 2 lines 33-43; Col. 9 lines 55-67).

Summary

23. Claims **1** and **9** are hereby rejected.
24. Claims **2** and **3** are hereby objected to for the reasons herein.
25. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:
 - a. US 6,569,662 B1 (27 May 2003) Tang *et al.* [SEQ ID NO: 111 thereof shares 100% sequence homology with SEQ ID NO: 1 of the instant application]
 - b. US 2003/0219744 (November 2003) Tang *et al.*
 - c. US 2003/0104529 (June 2003) Zhou *et al.*
 - d. US 2003/0045466 (March 2003) Tang *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
January 20, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER